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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/667,141	09/18/2003	Mario H. Skiadopoulos	NIHB-2203	7197
45160 7590 12/08/2009 WOODCOCK WASHBURN LLP CIRA CENTRE, 12TH FLOOR 2929 ARCH STREET PHILADELPHIA, PA 19104-2891				
EXAMINER				
BOESEN, AGNIESZKA				
ART UNIT		PAPER NUMBER		
1648				
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12/08/2009		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/667,141

Applicant(s)

SKIADOPOULOS ET AL.

Examiner

AGNIESZKA BOESEN

Art Unit

1648

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 September 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 67.73-76, 255 and 278 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 67.73-76, 255 and 278 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB06)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ ~~Notice of Informal Patent Application~~
- 6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(c), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(c) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 21, 2009 has been entered.

Claim Rejections - 35 USC § 112

Rejection of claims 75 and 76 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is **withdrawn** in view of Applicant's filing the Declaration with regard to the Biological Deposit.

New Rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim recites specific amino acid mutations in positions 948 and 1566 in the HPIV2 L polymerase without referring to a particular amino acid sequence SEQ ID NO:. Since there are different strains of the HPIV2 virus, as evidenced by Skidapoulos et al. (Journal of Virology 2003, Vol. 77, p. 270-279), the skilled artisan would expect that the amino acids at particular

positions in HPIV2 L polymerase may vary. Applicant is suggested to amend the claim to add a specific SEQ ID NO. Correction is required.

Claim Rejections - 35 USC § 102

Rejection of claims 67, 73, 74, 75, 255, and 278 are rejected under 35 U.S.C. 102(b) as being anticipated by Murphy *et al.* (WO 98/53078, herein, “Murphy”) **is withdrawn** in view of Applicant’s arguments.

Claim Rejections - 35 USC § 102/35 USC § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 67, 73, 74, 75, 255, and 278 are rejected under 35 U.S.C. 102(b)/35 U.S.C. 103(a) as being anticipated or obvious over Murphy *et al.* (WO 98/53078) in view of Kawano *et al.* (Virology, Vol. 284, p. 99-112) and as evidenced by Skidapoulos *et al.* (Journal of Virology 2003, Vol. 77, p. 270-279).

Murphy discloses an isolated, infectious, self-replicating, recombinant parainfluenza virus comprising a PIV major nucleocapsid (N) protein, a PIV nucleocapsid phosphoprotein (P),

a PIV large polymerase protein (L), and a partial or complete recombinant PIV genome or antigenome, wherein PIV genome is preferably a human PIV such as HPIV1, HPIV2 and HPIV3 (see page 7, lines 3-10, page 18, lines 22-39, and page 19, claims 1, 91, 96, 97). Murphy disclose a recombinant HPIV2 genome that incorporates a recombinantly-introduced attenuating mutations at one or more amino acid positions (see abstract, page 7, lines 33-39, page 8, lines 29-38, claims 102 and 107. Murphy discloses recombinant HPIV2 genome or antigenome incorporates one or more mutations of HPIV3 JS cp45 (see page 8, lines 20-29). Murphy discloses an isolated polynucleotide comprising partial or complete recombinant HPIV2 genome modified by one or more attenuating mutations and an expression vector comprising an operably linked transcriptional promoter, a polynucleotide sequence comprising partial or complete HPIV2 genome and a transcriptional terminator (see claims 1, 11, and 12).

Murphy does not expressly teach whether his HPIV2 genomes are polyhexameric or non-polyhexameric. Kawano teaches that both non-polyhexameric and polyhexameric HPIV2 genomes were known in the prior art (see page 106).

“Hence, at least three different RT±PCR clones of hPIV2 were sequenced, and one nucleotide deletion was found in 39-noncoding region of HN gene in previously reported hPIV2 sequence (data not shown). **This result indicated the total number of nucleotides in the correct hPIV2 genome was a multiple of six.**”

Present specification discloses that polyhexameric genomes are a property of natural HPIV2 isolates (specification [0253 and 0245]).

[0253] The discovery that **natural isolates of HPIV2 have polyhexameric length genomes**, that HPIV2 strictly follows the rule of six at the level of infectious virus, and that non-polyhexameric antigenomic cDNAs readily generate mutated virus and must be avoided, was unanticipated and provides the basis for the generation of recombinant HPIV2-based immunogenic compositions and viral vectors of defined sequence by reverse genetics.

Skidapoulos provides evidence that at least two strains of HPIV2, Greer and Venderbilt, isolated prior to the present invention, have polyhexameric genomes (page 275 and abstract).

We investigated the question of whether the natural genome length of HPIV2 conforms to the rule of six by determining the complete genomic sequence for three strains of HPIV2, namely the prototype **Greer strain and two recent HPIV2 isolates, V94 and V98**. Each of these strains has a **polyhexameric 15,654-nt genome length**, demonstrating that the **HPIV2 genome length is conserved and conforms to the rule of six**. A **polyhexameric antigenomic HPIV2/V94 cDNA** was used to recover a recombinant HPIV2/V94 with wt growth characteristics, and the length of the recovered virus was confirmed to be 15,654 nt. Full-length antigenomic HPIV2 cDNAs that were engineered to deviate from the rule of six by 1 to 5 nt yielded viruses that contained small nucleotide insertions or deletions that served to generate polyhexameric genomes. **These findings demonstrate that an HPIV2 polyhexameric genome can be generated from a cDNA that does not conform to the rule of six but that virus recovery appears to depend on the occurrence of spontaneous mutations that modify the length of the genome to conform to the rule of six**. These findings suggest

that HPIV2 has a strong preference for a polyhexameric genome.

Since Murphy does not teach what specific strain of HPIV2 he is using, it is not known whether Murphy's HPIV2 genome is polyhexameric or non-polyhexameric. Murphy must be using either polyhexameric or non-polyhexameric HPIV2. The polyhexameric HPIV2 in Murphy is an inherent property of HPIV2 as evidenced by Skidapoulos, who described this particular function of HPIV2.

The mere recitation of newly-discovered function or property, inherently possessed by things in the prior art, does not cause the claim drawn to those things to distinguish over the prior art (See *In re Best*, *Bolton*, and *Shaw* 195 USPQ 430 (CCPA 1977), *In re Schreiber* 44 USPQ2d 1429).

Even if Murphy has used the non-polyhexameric HPIV2, it would have been obvious to use the polyhexameric HPIV2 instead of the non-polyhexameric HPIV2 because Kawano teaches that the total number of correct HPIV2 genome is a multiple of six (see page 106).

All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim 76 is rejected under 35 U.S.C. 103(a) as being unpatentable over Murphy *et al.* (WO 98/53078, herein, “Murphy”) in view of Kawano *et al.* (Virology, Vol. 284, p. 99-112) and as evidenced by Skidapoulos *et al.* (Journal of Virology 2003, Vol. 77, p. 270-279) as applied to claims 67 above and further in view of Skiadopoulos *et al.* (Journal of Virology, 1999), and in view of Skiadopoulos *et al.* (Journal of Virology, 1998).

Murphy, Kawano and Skidapoulos (2003) teach the claimed invention as discussed above. Neither Murphy Kawano and Skidapoulos (2003) teach amino acid substitutions or deletions at residues 948 and/or 1566 of the HPIV2 L polymerase. However it would have been obvious to substitute amino acid residues at positions other than positions 942, 992, and 1558, in order to identify other amino acids positions within HPIV2 polymerase L that contribute to attenuation phenotypes. One of ordinary skill in the art would have been motivated to mutate polymerase L gene of HPIV2 in order to identify amino acid positions that contribute to attenuating mutations because Skiadopoulos (Journal of Virology, 1999) teaches that attenuating mutations in the L protein are dominant over those found in F protein (see page 1380). One would have had a reasonable expectation of success to identify other amino acids within L protein other than residues 942, 992, and 1558 that contribute to attenuating mutations because Skiadopoulos (Journal of Virology, 1998) teaches reverse-genetics systems that provide powerful tools for the characterization of attenuating mutations in viruses and make it possible to assemble a menu of attenuating mutations, are well established in the art (see page 1766). Thus the teachings of Murphy and Skiadopoulos obviate the current claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AGNIESZKA BOESEN whose telephone number is (571)272-8035. The examiner can normally be reached on 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Agnieszka Boesen/
Examiner, Art Unit 1648